Review of Pharmacokinetics, Pharmacodynamics and Toxicology for INDs and BLAs

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Goals

- Introduction to pharmacokinetics, pharmacodynamics and toxicology as applied to regulation of biological products
- Provide insights into the process of review, decision making, and roles of reviewers
- Talk will emphasize IND process as model for perspective and decision as applied to BLAs

Definitions

- Pharmacokinetics (Pk) - time dependent levels
- Pharmacodynamics (Pd) - dependent actions; aka pharmacology
- Toxicology (tox) – adverse effects
- IND – allows for interstate transport; intent to investigate (CFR 312)
- BLA – allows marketing (CFR 601)
- Study reports - typically contains nonclinical toxicology as well as clinical and nonclinical pharmacokinetics, and pharmacodynamics

Why Pk, Pd and Tox for INDs?

- Provide information regarding safety for products without prior human experience; when clinical data available, supplements and supportive
- Aimed at fundamental understanding of the therapeutic properties

Clinical Pharmacology and Toxicology Branch

- Primarily serves OTRR, provides reviews to OBRR and OVRR
- May assign to 1 or 2 reviews
  - If includes new nonclinical data then T reviewer
  - If nonclinical data not new, but includes clinical data for safety then D
  - If both new nonclinical and clinical then T and D
- Typical workload
  - 340 original INDs - 2/3 non-commercial INDs
  - 7900 amendments
  - 4 M.D.’s, 5 Ph.Ds
  - On average 1IND per week and 150 amendments

Administrative Issues

- Draft review by day 23 of date of receipt
- Hold telephone call to sponsor by day 29
- Hold telecon initiates 30 day to issue letter
- Internal working document is either Pharmacology or Clinical Pharmacology Worksheet
- Go into effect at 30 days unless stopped

Clinical Hold Originated for Clinical Pharmacology and Toxicology

- Least common among clinical holds items
- Large penalty for not getting it right
  - Frequently new studies requested
  - Impose delays in time and additional costs
  - May yield new issues

Raw Material

- Original studies
  - Pharmacology studies
  - Pharmacokinetic studies
  - Toxicology studies
  - Safety pharmacology studies
- Open scientific literature
- Closed regulatory – adverse event reporting

Personnel

- The reviewer and review team
- Supervisors and Division Director
- Experience and perspective

Review Process

- Team oriented – communications facilitated by e-mails and person-to-person
- General working philosophy
  - Clinical equipoise
  - Determine whether data “adequate” for proposed clinical study to be safe
- Major task is to separate relevant data from non-relevant information

Review Process

- Orientation - initial IND have risk – some risk can be identified and ‘quantitated’, but some remains unknown
- Scientifically and administratively complete
  - Data driven
  - Fair and objective
  - Decision clear and reasoning transparent
  - Documentation submitted to file and subject to further review

Every Submission is Unique

- A wide range of diseases and therapeutics
- Submission vary greatly
  - Quantity versus quality
  - Formal aspects, e.g., GLP or otherwise
  - Informative (versus advocacy)
  - Frequently depends on basic approach of sponsor – fixed ‘one size fits all’ or adaptive

The Two Approaches in Safety Evaluation

- Fixed-test oriented
  - Uses a series of studies thought adequate to assess safety
  - Commonly used
  - Tends to be inflexible and may ignore significant problems
  - Rarely used in the strict sense
  - Typically desired by sponsors

The Two Approaches in Safety Evaluation

- Adaptive approach
  - Selects and uses a custom blend of techniques to detect and evaluate risk; begins with risk identification
  - Flexible and changeable
  - Most scientifically oriented, but resources intensive particularly for time

Other Issues in Selecting an Approach

- Guidances
- Animal use
- Familiarity and expectations

Fixed-Test Oriented Approach

- Characteristics
  - Specified in advance and economies of scale
  - Design, components, analysis and outcome predetermined
- Example – USP biocompatibility, carcinogenicity bioassay, aspects of general toxicity tests, genotoxicity testing, generic drugs bioequivalence, general safety study

Fixed-Tests

- Disadvantages – other than for time not efficient on other resources not adaptable
  - Tends to considered a ‘requirement’
  - Genotoxicity testing versus ICH S6
  - Tends to favor quantity over quality
- Not always useful for biological products

Adaptive Approach

- Advantages - efficient in resources; highly effective
- Disadvantages
  - Requires knowledge, experience and judgment
  - Requires a priori decisions concerning risk
  - Needs common agreed upon categories of risk (low, moderate, high), risk causative, operational characteristics (frequency, consequences)

The Two Approaches

- Sponsor's often use a combination of adaptive and fixed approaches
- Some instances strictly require the adaptive approach – human specific therapeutics

IND Considerations

- Toxicity studies
- Clinical parameters
  - Initial dose
  - Dosing regimen
  - Dose escalation
  - Clinical population (number, disease, severity)
  - Monitoring (types, extent, frequency)

The Process of Decision Making

- Does the data as a whole make sense
- Interactions between disciplines for information provided
  - Between Pk, Pd and toxicology
  - Between product and medical
  - For examples, did the development of Ab's in the toxicity study obscure the detection of toxicity?

The Process of Decision Making

- Determination of safety
  - Are the known or anticipated risks evaluated?
  - Are the unknown risks considered (both in specific and through generally recognized procedures)?
  - The mental matrix – likelihood of occurrence, severity of effect, ability to detect, cause change (dis-continue drug, lower drug dose)

The Process of Decision Making

- Checks and balances – does the proposed study meet the criteria generally recognized to safeguard subjects?
  - Primary means of minimizing the effect of the unknown-unknown
  - Not too many at a time
  - Not too aggressive a dose escalation scheme or dosing regimen

Outcomes

- Go or no-go decision
- Go decision may entail modification to proposed study
  - Dose, frequency of dosing, patient population
  - Monitoring and reporting
  - Other issues – IB, informed consent
- Advice and recommendations

BLAs

- Role of Pk, Pd, tox becomes more specialized and narrow. Safety except in unique instances established through clinical studies
  - Mutagenicity, carcinogenicity, reproduction and development; special populations, e.g., renal impairment
  - Contributes of understanding and balance to risk for patients
  - Evolving areas
  - Labeling – clinical pharmacology; drug interactions; carcinogenesis, mutagenesis and impairment of fertility; pregnancy; nursing mothers; see CFR 201.

Comparability

- Why? - Intended to ensures continuity of preceding information and preclude the introduction of new, unevaluated factors (change in activity and safety profile)
- When? - Need for comparability demonstration may occur at various points in development
- How? - No absolute “formula”; types, nature and extent of comparability studies vary with the product and phase of clinical studies

Common Problems

- No data
- Redundancy and repetition
- Lack of critical analysis
- Unnecessary studies – substituting quantity for quality
  - Toxicity findings cannot be ignored

How to Get it Right

- PreINDs and preBLAs
  - Focused questions
  - Have the clinical protocol in mind
- Guidances
  - Read as guidances not rules; but don’t be too liberal
- Adopted a critical attitude
  - View conservatively and critically
  - Develop alternative strategies